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TITLE PAGE

Title:

Role of shoe cushioning, body mass and running biomechanics on injury risk: a study protocol for a randomised controlled trial

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ABSTRACT

Introduction: Repetitive loading of the musculoskeletal system is suggested to be involved in the underlying mechanism of the majority of running-related injuries (RRI). Accordingly, heavier runners are assumed to be at a higher risk of RRI. The cushioning system of modern running shoes is expected to protect runners again high impact forces, and therefore, RRI. However, the role of shoe cushioning in injury prevention remains unclear. The main aim of this study is to investigate the influence of shoe cushioning and body mass on RRI risk, while exploring simultaneously the association between running technique and RRI risk.

Methods and analysis: This double-blinded randomised controlled trial will involve about 800 healthy leisure-time runners. They will randomly receive one of two running shoe models that will differ in their cushioning properties (i.e. stiffness) by ~35%. The participants will perform a running test on an instrumented treadmill at their preferred running speed at baseline. They will then be followed-up prospectively over 6-month period, during which they will self-report all their sports activities as well as any injury in an internet-based database TIPPS (Training and Injury Prevention Platform for Sports). Cox regression analyses will be used to compare injury risk between the study groups, and to investigate the association between training, biomechanical and anatomical risk factors, and injury risk.

Ethics and dissemination: The study was approved by the National Ethics Committee for Research (Ref: 201701/02 v1.1). Outcomes will be disseminated through publications in peer-reviewed journals, presentations at international conferences, as well as articles in popular magazines and on specialised websites.

Trial registration number: NCT03115437

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Double-blinded randomised controlled trial (assessor and participant blinding) and intention-to-treat analysis.
- This study compares 2 shoe versions with widely differing cushioning properties while remaining within the cushioning range of models available on the market.
- A biomechanical analysis will be performed for each participant prior to the 6-month follow-up, which allows to investigate the association between running biomechanics and injury risk in a large cohort of runners.
- The running test will be carried out on a treadmill using a standardised protocol, which might not be reflective of the participants' habitual training conditions.

INTRODUCTION

Running is an increasingly popular form of physical activity. From a public health perspective, the promotion of leisure-time running might be a powerful strategy to combat the pandemic of physical inactivity worldwide,[1] and its consequence on non-communicable diseases.[2] Although regular running activity has a massive beneficial impact on health,[3] it also generates a relatively high number of injuries, especially at the lower limb.[4] The risk of sustaining a running-related injury (RRI) cancels out part of the benefits of running practice, since the long term consequences of injury include, among others, early-onset osteoarthritis,[5] a reduction of physical activity,[6] as well as an increase in health care costs.[7, 8] RRI incidence has remained high during the last 40 years, with an overall incidence rate ranging between 18.2% and 92.4%.[9] The role of footwear on RRI risk has been strongly emphasized ever since jogging became popular in the 1970s, but there is currently no evidence that developments in running shoe technology and new concepts regularly emerging on the market have helped to tackle the RRI burden.[10, 11]

Most RRI are overuse injuries, as they develop progressively over the kilometres run. The aetiology of these injuries is multifactorial,[12] which implies that to understand the mechanisms leading to injury, a holistic approach is warranted, including the study of a large set of potential risk factors. These factors could be classified as being related to training characteristics, running mechanics and anatomy of the runners. Some authors suggested that anatomical and biomechanical factors influence the tolerance to physical strain and thus the relationship between training load and injury occurrence.[13, 14]

Biological tissues such as bones, muscles and tendons can endure a certain amount of stress, provided that the product of stress level (e.g. intensity, external load) and the number of repetitions within a certain time period (e.g. strides, training sessions) remains below a threshold that is specific to each structure.[13] In running, the ground reaction force is the main external stress that acts on the body. Vertical ground reaction force (VGRF) is a biomechanical factor that has been extensively studied in

running.[15, 16] A recent meta-analysis found that the loading rate of the vertical ground reaction force was higher in patients with a history of stress fracture.[15] High impact-related variables were shown to increase the risk of bony and soft tissue injuries.[16] Moreover, running retraining interventions have proven their efficiency in modifying some VGRF parameters and decreasing pain, which suggest that running retraining represents an interesting paradigm to treat RRI.[17-19]

Since running biomechanics are associated with injury risk, any effect of shoe features on the running pattern and VGRF parameters deserve attention. Given that repetitive loading of the musculoskeletal system is an injury risk factor, cushioning has been one of the most extensively investigated shoe feature. The shock absorption properties of footwear mainly result from the materials used in the sole (i.e. their type, density, structure and combination), as well as from the geometry of the shoe (i.e. the midsole thickness and the design of inserts). One of the most popular approaches has been to change the hardness of the shoe midsole.[20-22] Overall, the studies investigating the effect of shoe cushioning on VGRF did not provide consistent results. In theory, peak impact forces should be reduced by softer or more compliant shoes,[23] which was indeed confirmed in some in vivo studies.[24, 25] Conversely, some investigations did not find any effect of cushioning,[26] or reported increased peak impact forces in softer shoes.[20, 27] Recently, a large cross sectional study revealed that softer midsole hardness was associated with higher vertical force impact peak.[20] Unfortunately, very few studies investigated the association between shoe cushioning and injury risk.[28, 29] Therefore, the role of shoe cushioning systems in RRI prevention remains unknown.

Body mass index (BMI) has been associated with injury risk in novice,[30, 31] as well as in recreational runners,[28] though other results suggest a protective effect of BMI.[9] It is common belief that individuals with higher BMI have a higher injury risk, because of the increased physical stress that results from extra body weight. Surprisingly, body mass as such has hardly ever been considered as a potential risk factor for running injury.[9]

Surprisingly, the literature on the association between single shoe features and RRI risk is still poor.[11, 32, 33] Until now, no relationship has been found between the cushioning properties of modern running shoes and RRI risk,[28] but body mass should be taken into account here. Therefore, the main purpose of this study is to investigate the association between shoe cushioning and body mass on the one hand, and RRI risk on the other hand in recreational runners. The secondary aims are to identify which of the running technique-related characteristics (timing variables and VGRF parameters) are associated with injury risk, as well as with the cushioning properties of the shoes. The following hypotheses (H) will be tested:

H1. Running shoes with greater stiffness are associated with a higher injury risk in leisure-time runners.

H2. High body mass is associated with a higher injury risk in leisure-time runners.

H3. Runners with a high body mass experience a lower injury risk in shoes with greater stiffness.

H4. A higher step length, a lower step frequency, and higher peak vertical impact forces are associated with a higher injury risk.

H5. Running shoes with greater stiffness will be associated with higher vertical impact peak forces and a shorter contact time.

H6. High body mass will be associated with higher peak vertical impact forces, increased contact time, increased duty factor, and decreased step frequency.

Furthermore, exploratory risk factor analyses will be performed on the biomechanical variables obtained from the running analysis, anthropometric measurements, running experience, and habitual running speed. The focus of the analyses is the effect modification of body mass and other above mentioned risk factors on the association between shoe cushioning and injury risk.

METHODS AND ANALYSIS

Trial design

The design of this study is a randomised controlled trial with a 6-month follow-up and a biomechanical analysis of running pattern at baseline. The study is based on the comparison between

2 running shoe prototypes, which only differ with respect to the cushioning (i.e. stiffness). The cushioning properties of both shoe versions are within the range of those from available models on the market. Running footwear is provided by a renowned sport equipment manufacturer. The main outcome is RRI (cf. definition below). The participants as well as the assessors are blinded to group allocation. The design of the trial is illustrated in Figure 1. The protocol conforms to the Recommendations for Interventional Trials (SPIRIT) and has been registered on https://clinicaltrials.gov/ (NCT03115437, 11/04/2017).

Insert Figure 1 about here

Study population

The target population is leisure-time runners, regardless of running experience, fitness level, or body mass. Participants will be recruited through advertisements in local newspapers, social media, running magazines and press releases within the country during the months of September 2017 to January 2018. Healthy volunteers will be considered eligible if they are aged between 18 and 65 years and capable of performing 15 minutes of consecutive running. Volunteers will be excluded in case of any contraindication to perform running activity, prior (<12 months) surgery at the lower limbs or lower back region, use of orthopaedic insoles for running activities, or current RRI. Additionally, the participants will have to agree on the following requirements: 1) to practice running at least once a week, 2) to use the provided study shoes for all their running sessions, and 3) to report, at least once per week, all sports activities, as well as any injury or pain experienced during the follow-up period on an internet-based database called TIPPS (Training and Injury Prevention Platform for Sports, www.tipps.lu). Volunteers first have to create a personal account on TIPPS, pre-register to the study via their personal account, and answer an online inclusion/exclusion questionnaire as well as a baseline questionnaire. Answers to both questionnaires will be assessed by the investigators during the initial visit.

Randomisation

Participants must understand and agree on the randomized design of the study. Those who meet the eligibility criteria and sign the informed consent form will be randomly allocated to one of the two study arms. They will be stratified according to their sex, which is known to influence body mass as well as many other anthropometric characteristics. Therefore, two pre-established randomisation lists (block size = 40) will be prepared by a statistician not involved in any other part of the study before the beginning of the recruitment. To ensure allocation concealment, the study groups and shoes will be coded and the randomisation lists will be uploaded in the TIPPS system by an IT specialist who will not be involved in any other part of the study. Then, the TIPPS system will provide the investigator in charge of the recruitment with a study group number for each participant, according to the randomisation lists. The investigator will upload the shoe number according to shoe size chosen and study arm so that a cross validation will be performed by the electronic system. The investigators in charge of the recruitment, the follow-up and data quality check, as well as the participants, will be blinded regarding the shoe version distributed. The shoe code will be broken after completion of data analysis.

Intervention

The study shoes are prototypes and will be anonymized for the purpose of this trial. The sole of the shoes will be customized so that the two running shoe prototypes will be exactly the same (same midsole, same outsole, same upper), except for their cushioning properties which will differ by about 35%, while remaining within the range of the models available on the market (stiffness: ~53-97 N/mm). The differences in cushioning properties between shoe versions will be created by modifying the midsole material, i.e. chemistry, density, and therefore the hardness of the Ethylene Vinyl Acetate (EVA) foam. In order to provide accurate data on the technical specifications (i.e. shoe stiffness) of each prototype, a set of 40 shoes (10 pairs per condition) will be tested for cushioning properties by the manufacturer according to a standardized protocol (Impact test: ASTM1614, Procedure A).[34]

Data collection

Baseline questionnaire

During the online registration process, the participants have to fill in a baseline questionnaire to report information regarding running experience, training habits, recent running competitions performed and injury history. A standardised questionnaire concerning the risk of sports participation must also be completed by the volunteers. Every participant responding positively to any of the symptom-based questions or to more than one risk factor will be invited for a clearance check by a sports medical doctor prior to the test.

Biomechanical testing

The biomechanical running analysis will be performed on an instrumented treadmill (M-Gait, Motekforce Link Amsterdam, The Netherlands) in the study shoes, according to the random allocation. The test (10 minutes) consists of a 5-minute warm-up followed by a 5-minute run at the self-declared preferred (habitual) running speed. Two records of 45 seconds will be obtained over the last 2 minutes of the test. No data will be recorded during the first 8 minutes, which was shown to be enough time to provoke short-term adaptations of running style with respect to the shoe type.[21, 35] Additionally, the participants who reported a preferred running speed equal to 10 km/h (+/- 1 km/h) will be invited to perform a second test at the end of the follow-up period. This second test will consist in 10 minutes of running in each shoe model. Records will be obtained during the last 2 minutes of each run. This will allow a within subject analysis of the shoe effect on running biomechanics at a standardised speed.

Table 1: Biomechanical variables of interest.

Variable	Abbreviation	Unit	Normalization
Step frequency	SF	[Steps.min^{-1}]	/
Contact time	CT	[ms]	/
Flight time	FT	[ms]	/
Duty factor	DF	[%]	/

Step length	SL	[m]	[%LL]
Vertical Impact Peak Force	VIPF	[N]	[$N.kg^{-1}$]
Peak Vertical Force	PVF	[N]	[$N.kg^{-1}$]
Vertical Instantaneous Loading Rate	VILR	[$N.s^{-1}$]	[$N.kg^{-1}.s^{-1}$]
Vertical Average Loading Rate	VALR	[$N.s^{-1}$]	[$N.kg^{-1}.s^{-1}$]
Peak Power	PP	[W]	[$W.kg^{-1}$]
Time to Peak Force	TPF	[ms]	/
Leg stiffness	Kleg	(kN/m)	/
Vertical stiffness	Kvert	(kN/m)	/

N: Newton, min: minute, ms: millisecond, m: meter, LL: leg length, kg: kilogram, W: Watt.

Anthropometric measures

The body mass of each participant will be measured before the treadmill running test in a stationary position. Also, the participants will have to report their body mass on a monthly basis onto their TIPPS account. Pop-up windows will inform the participants when an update is needed. In clinical settings, leg length is usually assessed as the measure between the anterior superior iliac spine and the medial malleolus, and is referred to as the "direct" clinical method.[36] The measurements will be performed on both legs and the average value will be used for the normalisation of step length. Additionally, the distance between the great trochanter and the ground will be measured to assess leg stiffness.[37] Body composition will be evaluated by bioelectrical impedance analysis (Tanita SC-240 MA). The proportion of fat mass will be included in the analyses as a potential confounder for the association between body mass and injury risk.

Data on exposure

Data on running practice will be collected using the TIPPS system.[28, 38] Required information in the sport activity report includes the type of activity, context, duration, subjectively perceived intensity, distance, shoe pair used, running surface (hard or soft), and whether the participant had experienced any pain during the session forcing him/her to reduce practice volume or intensity, or to interrupt the practice. Session intensity is determined using the Borg's rating of perceived exertion scale, a subjective 10-point scale.[39]

Data on outcome

The primary outcome is first-time RRI. A consensus definition of RRI in recreational runners has been recently published.[40] The definition of RRI is a "running-related (training or competition) musculoskeletal pain in the lower limbs that causes a restriction on or stoppage of running (distance, speed, duration, or training) for at least 7 days or 3 consecutive scheduled training sessions, or that requires the runner to consult a physician or other health professional."

In previous studies, an RRI was defined as "any physical pain located at the lower limbs or lower back region, sustained during or as a result of running practice and impeding planned running activity for at least 1 day" (time-loss definition).[14, 28, 32, 33, 38] All injuries reported by the participants during the follow-up will be assessed according to each of the two definitions presented here above. The consensus definition will be considered as the reference, while a sensitive analysis will reveal if the results would be impacted when using the former definition of RRI.

Similarly to uploading a training session or competition, the TIPPS provides a complete yet easy to fill in questionnaire when reporting an injury. Information regarding the following is required: injury date, context, sports discipline, injury mechanism (acute or progressive), anatomical location, type of injury, description and estimated return date. RRI will be classified according to the Orchard Sports Injury Classification System version 10 (OSICS-10).[41] Injury severity will be measured in days of modified or interrupted training.

Follow-up

Given that the participants are required to practice running at least once a week, individual e-mail reminders will be sent to the participants who do not provide the system with any data for the previous week. Personal phone calls will be made if the participants do not react to the e-mail reminders and if the reported information in either the training log or on the injury form is found to be inconsistent.

Injury data will be systematically checked by one of the investigators for completeness and coherence. Participants who do not complete their entire running calendar with weekly information will be contacted by one of the investigators to ensure that a RRI is not the reason for non-compliance or dropping out. The intervention period will last six months, allowing enough time for the participants to cover a large distance with the study shoes.

Sample size

A sample size calculation for Cox regression was used to determine the number of participants needed for the primary hypothesis of the study. With an alpha of 0.05 and a power of 80%, an average injury rate of 30%,[14, 32, 33] an expected HR=1.50 between groups, 50% of participants randomised to each shoe group and an expected drop-out rate of 20%, the total number of participants required is 802.

A within subject analysis will be performed on a subgroup of participants to investigate the effect of shoe condition on VGRF. A total sample of 39 participants will be required to detect a difference of 0.16 body weight (standard deviation: 0.25 body weight)[20] between shoe conditions with 80% power and a significant level of 5%.

Statistical analysis

Descriptive data for the personal, anthropometric, biomechanical and training-related characteristics will be presented as count and percentage for dichotomous variables, and as mean and standard deviation, or as median and range, respectively, for normally and non-normally distributed continuous variables. Average sport-related characteristics will be computed for each participant over their specific period of observation. Shock absorption properties of the two types of shoes will be compared using a Student's t test. A two-way analysis of variance (ANOVA) will be used to determine whether any difference in running biomechanics results from the shoe cushioning properties or body mass.

Cox proportional hazards regressions will be used to compute the hazard rates (HR) in the exposure groups, using first-time injury as the primary outcome. Date of inclusion (baseline evaluation date) and date of injury or of censoring will be basic data used to calculate the time at risk, which is expressed in hours spent running and defined as the time-scale.[31] A participant will be right-censored if injury unrelated to running or severe disease caused a modification of the running plan, or at the end of follow-up. The assumption of proportional hazards will be evaluated by log-minus-log plots.

Unadjusted Cox regressions will be performed to present the crude estimates of HRs for shoe model, body mass and other potential risk factors such as running biomechanics variables and training-related characteristics. Body mass is an exposure that can change over time (time-dependent covariate). This means that each participant could move between exposure states continuously (every month in our study). A delayed entry will be used in the unadjusted Cox regression model for body mass.[42]

Subsequently, the variables with a P value <0.200 will be included in the adjusted Cox regression analysis to determine whether shoe cushioning and/or body mass are associated with injury risk, controlling for potential confounders. The recommendation for using at least 10 injuries per predictor variable included in the Cox regression analysis will be strictly followed.[43]

Finally, to investigate if the effect of shoe cushioning on RRI risk is modified by body mass, a stratified analysis will be performed using the median value of body mass as cut-off. HRs and their 95% confidence intervals (CI) will be determined within each stratum.[44] All analyses will be performed using STATA/SE version 14.

DISCUSSION

It is common belief that shoe cushioning technology protects the runner against harmful consequences of repetitive high-load impacts. Therefore, heavier runners are generally advised to use footwear with adapted shock absorption properties. Surprisingly, few studies have investigated the impact of shoe cushioning on injury risk.[28, 29] These studies did not provide any evidence on the beneficial effect of increased shock absorption properties. However, none of them included anthropometric measures in their analyses. Also, one study compared different types of insoles added in the shoes,[29] while the other compared two versions of a standard running shoe with a limited difference in midsole hardness (~15%).[28] Other study limitations such as the sample size (n<250)[28] or the study population (Royal Air Force recruits)[29] suggest that these results should be interpreted with caution. The evidence on the association between running shoe cushioning and RRI is still poor and inconclusive. One of the main reasons is the practical constraint of investigations trying to combine biomechanical analyses with a long-term prospective follow-up in a large number of runners.[11] This study is the first randomised controlled trial investigating the influence of shoe cushioning on RRI risk including an evaluation of running technique in all participants. The results will provide information on the real benefits provided by additional cushioning, as well as on the mechanisms that might explain any potential preventive effect.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the Declaration of Helsinki and the Medical Research Involving Human Subjects Act. Also, the study protocol was approved by the National Ethics Committee for Research (Ref: 201701/02 v1.1). Written informed consent will be obtained from all participants. All collected data will be stored electronically using a coding system. This will ensure that the data is used in the strictest confidence and will not reveal the identity of the participants. Collected raw data will not be passed on to unauthorised third parties. Results presented or published in articles and reports will be depicted in general terms, to maintain participant anonymity. Electronic data will be stored on a secure server in data files only accessible to the project leader and co-investigators of the project. A notification of this study was sent to the National Data Protection Agency (CNPD). Study results will be submitted for publication in peer-reviewed journals and for presentation at international conferences. Furthermore, we aim to disseminate our results through popular specialised magazines and websites.

Contributors - LM, ND, AU and DT contributed to the study conception and study design. LM is the main investigator, wrote the article with input from other investigators, and will be responsible for the acquisition and analysis of the data. ND will be responsible for the shoe design, production and testing. LM and DT will be responsible for data interpretation and manuscript drafting. ND, AU and DT commented on the various versions of the study protocol. All authors approved the final manuscript.

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Competing interests – A research partnership agreement was signed between Decathlon and the LIH. ND is employed at Decathlon. Decathlon will not be involved in the collection, management, analysis and interpretation of data. LM, DT and AU may not gain or lose financially from the results of the study in any way.

Ethics approval - All procedures were approved by the National Ethics Committee for Research (Ref: 201701/02 v1.1).

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FIGURE LEGEND

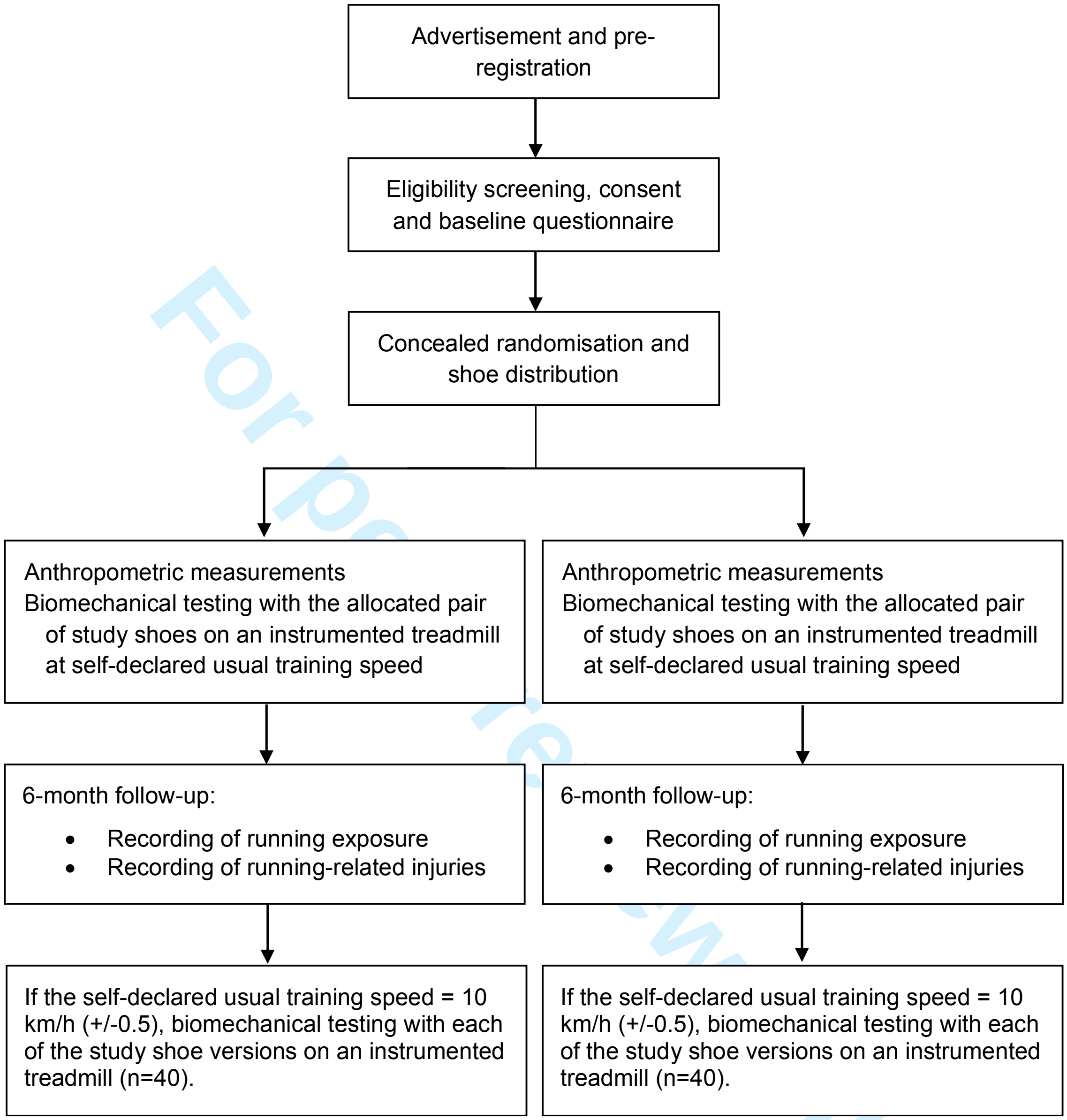
Figure 1: Trial design.

SUPPLEMENTARY FILES

Supplementary file 1: SPIRIT Checklist

Supplementary file 1: Study schedule

Figure 1:


Advertisement and pre-registration
Eligibility screening, consent and baseline questionnaire
Concealed randomisation and shoe distribution
Anthropometric measurements
Biomechanical testing with the allocated pair of study shoes on an instrumented treadmill at self-declared usual training speed
Anthropometric measurements
Biomechanical testing with the allocated pair of study shoes on an instrumented treadmill at self-declared usual training speed
6-month follow-up:
• Recording of running exposure
• Recording of running-related injuries
6-month follow-up:
• Recording of running exposure
• Recording of running-related injuries
If the self-declared usual training speed = 10 km/h (+/-0.5), biomechanical testing with each of the study shoe versions on an instrumented treadmill (n=40).
If the self-declared usual training speed = 10 km/h (+/-0.5), biomechanical testing with each of the study shoe versions on an instrumented treadmill (n=40).

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 5: clinicaltrials.gov (NCT03115437)
	2b	All items from the World Health Organization Trial Registration Data Set	/
Protocol version	3	Date and version identifier	Page 7
Funding	4	Sources and types of financial, material, and other support	Page 15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 15
	5b	Name and contact information for the trial sponsor	Page 15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 15

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n.a.
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Pages 4 and 5
	6b	Explanation for choice of comparators	Pages 5 and 4
Objectives	7	Specific objectives or hypotheses	Page 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 6 and 7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 11-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n.a.

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 9 and 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 and Suppl. file 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 8
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Pages 9 to 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 11
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pages 12 and 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Pages 12 and 13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Pages 12 and 13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	/
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	/
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	/
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Pages 14 and 15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	/
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 14
	31b	Authorship eligibility guidelines and any intended use of professional writers	/
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 3

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

Supplementary file 2: Schedule of enrolment, interventions, and assessments for the study

	STUDY PERIOD							
	Enrolment	**Allocation**	**Post-allocation: For every sport activity**					**Close-out**
TIMEPOINT	$-t_1$	**0**	t_1	t_2	t_3	t_4	*etc.*	***6 Months***
ENROLMENT								
Eligibility screen	X							
Informed consent	X							
Baseline Questionnaire	X	X						
Allocation		X						
Shoe distribution		X						
Running analysis		X						
INTERVENTIONS								
[Intervention A]								
[Intervention B]								
ASSESSMENTS								
Running experience	X	X						
Running regularity	X	X						
Typical running frequency	X	X						
Typical running distance	X	X						
Training running speed	X	X						
Type of running	X	X						
Competition participation	X	X						
Last event distance	X	X						
Favourite running distance	X	X						
Best time on 5 km / 10km	X	X						
Previous injury	X	X						

Height	X	X						
Body mass	X	X						
Leg length	X	X						
% fat tissue	X	X						
Step frequency	X	X						
Contact time	X	X						
Flight time	X	X						
Duty factor	X	X						
Step length	X	X						
Vertical Impact Peak Force	X	X						
Peak Vertical Force	X	X						
Vertical Instantaneous Loading Rate	X	X						
Vertical Average Loading Rate	X	X						
Peak Power	X	X						
Time to Peak Force	X	X						
Leg stiffness	X	X						
Vertical stiffness	X	X						
Sports discipline			X	X	X	X	etc.	
Duration			X	X	X	X	etc.	
Distance (if applicable)			X	X	X	X	etc.	
Perceived Exertion			X	X	X	X	etc.	
Shoe used (if running)			X	X	X	X	etc.	
Surface (if running)			X	X	X	X	etc.	
Pain*			X	X	X	X	etc.	
Injury**			X	X	X	X	etc.	

*The pain did not stop the participant from continuing normal training
**The participants had to adapt or interrupt their training accordingly

Free Informed Consent

Title:
Institution:
Project manager:
Research assistant:
Head of unit:

1. I declare to have read the above-described information and accept to voluntarily participate in the study "Effects of bodyweight and shoe cushioning on injury risk and running biomechanics: A randomised control trial" conducted by the SMRL.
2. I accept that my data shall be used and communicated to the commercial partner for strictly scientific purposes once it has been pseudonymised (coded).
3. I received a copy of the present signed informed consent document, as well as the general information intended for athlete participants. I received a clear description of the purpose and the nature of the study and I am aware of what is expected of me as a participant in this study. I have had enough time and the opportunity to ask questions about the study; all my questions have been met with a satisfactory answer.
4. I am free to retire from the study at any time without justification. By doing so I will not suffer any material or moral damage.
5. I agree that the results of this study can be subject to public talks or scientific publication.
6. I voluntarily consent to participate in this study and I fully understand what kind of data will be gathered during the study.
7. I preserve/abide the rights of access, deletion or modification of my personal data. Any personal information will be kept confidential and protected in agreement with the modified personal data protection act of August 2nd 2002. I can exercise that right via the project manager.

The responding signatory freely consents to participate in the above mentioned study

Name and First Name of the respondent: ....

Signature of the respondent: ……………………………………………………………………………

Name and signature of the project manager: ……………………………………………………………..

Place and date: …………………………..

BMJ Open

Shoe cushioning, body mass and running biomechanics as risk factors for running injury: a study protocol for a randomised controlled trial

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Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Public health
Keywords:	Sports injury prevention, Footwear, Impact forces, EPIDEMIOLOGY

TITLE PAGE

Title:

Shoe cushioning, body mass and running biomechanics as risk factors for running injury: a study protocol for a randomised controlled trial

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ABSTRACT

Introduction: Repetitive loading of the musculoskeletal system is suggested to be involved in the underlying mechanism of the majority of running-related injuries (RRI). Accordingly, heavier runners are assumed to be at a higher risk of RRI. The cushioning system of modern running shoes is expected to protect runners again high impact forces, and therefore, RRI. However, the role of shoe cushioning in injury prevention remains unclear. The main aim of this study is to investigate the influence of shoe cushioning and body mass on RRI risk, while exploring simultaneously the association between running technique and RRI risk.

Methods and analysis: This double-blinded randomised controlled trial will involve about 800 healthy leisure-time runners. They will randomly receive one of two running shoe models that will differ in their cushioning properties (i.e. stiffness) by ~35%. The participants will perform a running test on an instrumented treadmill at their preferred running speed at baseline. They will then be followed-up prospectively over a 6-month period, during which they will self-report all their sports activities as well as any injury in an internet-based database TIPPS (Training and Injury Prevention Platform for Sports). Cox regression analyses will be used to compare injury risk between the study groups and to investigate the association between training, biomechanical and anatomical risk factors, and injury risk.

Ethics and dissemination: The study was approved by the National Ethics Committee for Research (Ref: 201701/02 v1.1). Outcomes will be disseminated through publications in peer-reviewed journals, presentations at international conferences, as well as articles in popular magazines and on specialised websites.

Trial registration number: NCT03115437

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Double-blinded randomised controlled trial (assessor and participant blinding) and intention-to-treat analysis.
- This study compares 2 shoe versions with widely differing cushioning properties while remaining within the cushioning range of models available on the market.
- A biomechanical analysis will be performed for each participant prior to the 6-month follow-up, which allows to investigate the association between running biomechanics and injury risk in a large cohort of runners.
- The running test will be carried out on a treadmill using a standardised protocol, which might not be reflective of the participants' habitual training conditions.

INTRODUCTION

Running is an increasingly popular form of physical activity. From a public health perspective, the promotion of leisure-time running might be a powerful strategy to combat the pandemic of physical inactivity worldwide,[1] and its consequence on non-communicable diseases.[2] Although regular running activity has a massive beneficial impact on health,[3] it also generates a relatively high number of injuries, especially at the lower limb.[4] The risk of sustaining a running-related injury (RRI) cancels out part of the benefits of running practice, since the long term consequences of injury might include, among others, increased risk of osteoarthritis,[5] a reduction of physical activity,[6] as well as an increase in health care costs.[7, 8] RRI incidence has remained high during the last 40 years, with an overall incidence rate ranging between 18.2% and 92.4%.[9] The role of footwear on RRI risk has been strongly emphasized ever since jogging became popular in the 1970s, but there is currently no evidence that developments in running shoe technology and new concepts regularly emerging on the market have helped to tackle the RRI burden.[10-12]

Most RRI are overuse injuries, as they develop progressively over the kilometres run. The aetiology of these injuries is multifactorial,[13] which implies that to understand the mechanisms leading to injury, a holistic approach is warranted, including the study of a large set of potential risk factors. These factors could be classified as being related to training characteristics, running mechanics and anatomy of the runners. Some authors suggested that anatomical and biomechanical factors influence the tolerance to physical strain and thus the relationship between training load and injury occurrence.[14, 15]

Biological tissues such as bones, muscles and tendons can endure a certain amount of stress, provided that the product of stress level (e.g. intensity, external load) and the number of repetitions within a certain time period (e.g. strides, training sessions) remains below a threshold that is specific to each structure.[14] In running, the ground reaction force is the main external stress that acts on the body. Vertical ground reaction force (VGRF) is a biomechanical factor that has been extensively studied in

running.[16, 17] A recent meta-analysis found that the loading rate of the vertical ground reaction force was higher in patients with a history of stress fracture.[16] High impact-related variables were shown to increase the risk of bony and soft tissue injuries.[17] Moreover, running retraining interventions have proven their efficiency in modifying some VGRF parameters and decreasing pain, which suggest that running retraining represents an interesting paradigm to treat RRI.[18-20] Other biomechanical factors such as step length,[21] step frequency [22] or leg stiffness [23] have previously been suggested as potential biomechanical risk factors for RRI, yet no causal relationship has been established.

Since running biomechanics are associated with injury risk, any effect of shoe features on the running pattern and VGRF parameters deserve attention. Given that repetitive loading of the musculoskeletal system is an injury risk factor, cushioning has been one of the most extensively investigated shoe features. The shock absorption properties of footwear mainly result from the materials used in the sole (i.e. their type, density, structure and combination), as well as from the geometry of the shoe (i.e. the midsole thickness and the design of inserts). One of the most popular approaches has been to change the hardness of the shoe midsole.[24-26] Overall, the studies investigating the effect of shoe cushioning on VGRF did not provide consistent results. In theory, peak impact forces should be reduced by softer or more compliant shoes,[27] which was indeed confirmed in some in vivo studies.[28, 29] Conversely, some investigations did not find any effect of cushioning,[30] or reported increased peak impact forces in softer shoes.[24, 31] Recently, a large cross sectional study revealed that softer midsole hardness was associated with higher vertical force impact peak.[24] Unfortunately, very few studies have investigated the association between shoe cushioning and injury risk.[32, 33] In a previous randomised controlled trial, midsole hardness was not associated with RRI risk. However, the difference in shoe stiffness between the shoe conditions was limited (15%).[32] Therefore, the role of shoe cushioning systems in RRI prevention remains unclear.

Body mass index (BMI) has been associated with injury risk in novice,[34, 35] as well as in recreational runners,[32] though other results suggest a protective effect of BMI.[9] It is common belief that individuals with higher BMI have a higher injury risk, because of the increased physical stress that results from extra body weight. Surprisingly, body mass as such has hardly ever been considered as a potential risk factor for running injury.[9]

Surprisingly, the literature on the association between single shoe features and RRI risk is still poor.[11, 36, 37] Until now, no relationship has been found between the cushioning properties of modern running shoes and RRI risk,[32] but body mass should be taken into account here. Therefore, the main purpose of this study is to investigate the association between shoe cushioning and body mass on the one hand, and RRI risk on the other hand in recreational runners. The secondary aims are to identify which of the running technique-related characteristics (timing variables and VGRF parameters) are associated with injury risk, as well as with the cushioning properties of the shoes. Shoe cushioning will be characterised by the stiffness at the heel (N/mm) and quantified by standardised impact test.[38] The following hypotheses (H) will be tested:

H1. Running shoes with greater stiffness are associated with a higher injury risk in leisure-time runners.

H2. High body mass is associated with a higher injury risk in leisure-time runners.

H3. Runners with a high body mass experience a lower injury risk in shoes with greater stiffness.

H4. A higher step length, a lower step frequency, and higher vertical loading rate are associated with a higher injury risk.

H5. Running shoes with greater stiffness will be associated with higher vertical loading rate and a shorter contact time.

H6. High body mass will be associated with higher vertical loading rate, increased contact time, increased duty factor, and decreased step frequency.

Furthermore, exploratory risk factor analyses will be performed on the biomechanical variables obtained from the running analysis, anthropometric measurements, running experience, and habitual running speed. The focus of the analyses is the effect modification of body mass and other above mentioned risk factors on the association between shoe cushioning and injury risk.

METHODS AND ANALYSIS

Trial design

The design of this study is a randomised controlled trial with a 6-month follow-up and a biomechanical analysis of running pattern at baseline. The study is based on the comparison between 2 running shoe prototypes, which only differ with respect to the cushioning (i.e. stiffness). The cushioning properties of both shoe versions are within the range of those from available models on the market. Running footwear is provided by a renowned sport equipment manufacturer. The main outcome is RRI (cf. definition below). The participants as well as the assessors are blinded to group allocation. The design of the trial is illustrated in Figure 1. The protocol conforms to the Recommendations for Interventional Trials (SPIRIT, supplementary files 1 and 2) and has been registered on https://clinicaltrials.gov/ (NCT03115437, 11/04/2017).

Insert Figure 1 about here

Study population

The target population is leisure-time runners, regardless of running experience, fitness level, or body mass. Participants will be recruited through advertisements in local newspapers, social media, running magazines and press releases within the country during the months of September 2017 to January 2018. Healthy volunteers will be considered eligible if they are aged between 18 and 65 years and capable of performing 15 minutes of consecutive running. Volunteers will be excluded in case of any contraindication to perform running activity, prior (<12 months) surgery or major trauma to the lower limbs or lower back region, any running impeding injury over the previous months, or use of orthopaedic insoles for running activities. Additionally, the participants will have to agree on the following requirements: 1) to practice running at least once a week, 2) to use the provided study shoes for all their running sessions, and 3) to report, at least once per week, all sports activities, as well as any injury or pain experienced during the follow-up period on an internet-based database called TIPPS (Training and Injury Prevention Platform for Sports, www.tipps.lu). Volunteers first have to create a personal account on TIPPS, pre-register to the study via their personal account, and answer an online inclusion/exclusion questionnaire as well as a baseline questionnaire. Answers to both questionnaires will be assessed by the investigators during the initial visit.

Randomisation

Participants must understand and agree on the randomized design of the study. Those who meet the eligibility criteria and sign the informed consent form will be randomly allocated to one of the two study arms. They will be stratified according to their sex, which is known to influence body mass as well as many other anthropometric characteristics. Therefore, two pre-established randomisation lists (block size = 40) will be prepared by a statistician not involved in any other part of the study before the beginning of the recruitment. To ensure allocation concealment, the study groups and shoes will be coded and the randomisation lists will be uploaded in the TIPPS system by an IT specialist who will not be involved in any other part of the study. Then, the TIPPS system will provide the investigator in charge of the recruitment with a study group number for each participant, according to the randomisation lists. The investigator will upload the shoe number according to shoe size chosen and study arm so that a cross validation will be performed by the electronic system. The investigators in charge of the recruitment, the follow-up and data quality check, as well as the participants, will be blinded regarding the shoe version distributed. The shoe code will be broken after completion of data analysis.

Intervention

The study shoes are prototypes and will be anonymized for the purpose of this trial. The sole of the shoes will be customized so that the two running shoe prototypes will be exactly the same (same midsole, same outsole, same upper), except for their cushioning properties which will differ by about

35%, while remaining within the range of the models available on the market (stiffness: ~53-97 N/mm). The differences in cushioning properties between shoe versions will be created by modifying the midsole material, i.e. chemistry, density, and therefore the hardness of the Ethylene Vinyl Acetate (EVA) foam. In order to provide accurate data on the technical specifications (i.e. shoe stiffness) of each prototype, a set of 40 shoes (10 pairs per condition) will be tested for stiffness properties by the manufacturer according to a standardized protocol (Impact test: ASTM1614, Procedure A).[38]

Data collection

Baseline questionnaire

During the online registration process, the participants have to fill in a baseline questionnaire to report information regarding running experience, training habits, recent running competitions performed and injury history. A standardised questionnaire concerning the risk of sports participation must also be completed by the volunteers (Supplementary file 3). Every participant responding positively to any of the symptom-based questions or presenting more than one cardiovascular risk factor will be invited for a clearance check by a sports medical doctor prior to the test.

Biomechanical testing

The biomechanical running analysis will be performed on an instrumented treadmill (M-Gait, Motekforce Link Amsterdam, The Netherlands) in the randomly allocated study shoes. The test (10 minutes) consists of a 5-minute warm-up followed by a 5-minute run at the self-declared preferred (habitual) running speed. Two records of 45 seconds will be obtained at a sampling rate of 1 kHz over the last 2 minutes of the test. No data will be recorded during the first 8 minutes, which was shown to be enough time to provoke short-term adaptations of running style with respect to the shoe type.[25, 39] The main biomechanical variables of interest are presented in table 1.

Table 1: Biomechanical variables of interest.

Variable	Abbreviation	Unit	Normalization

Step frequency	SF	[Steps.min^{-1}]	/
Contact time	CT	[ms]	/
Flight time	FT	[ms]	/
Duty factor	DF	[%]	/
Step length	SL	[m]	[%LL]
Vertical Impact Peak Force	VIPF	[N]	[N.kg^{-1}]
Peak Vertical Force	PVF	[N]	[N.kg^{-1}]
Vertical Instantaneous Loading Rate	VILR	[N.s^{-1}]	[N.kg^{-1}.s^{-1}]
Vertical Average Loading Rate	VALR	[N.s^{-1}]	[N.kg^{-1}.s^{-1}]
Peak Power	PP	[W]	[W.kg^{-1}]
Time to Peak Force	TPF	[ms]	/
Leg stiffness	Kleg	(kN/m)	/
Vertical stiffness	Kvert	(kN/m)	/

N: Newton, min: minute, ms: millisecond, m: meter, LL: leg length, kg: kilogram, W: Watt.

Anthropometric measures

Body mass and height of each participant will be measured barefoot and in running clothes before the treadmill running test. Also, the participants will have to report their body mass on a monthly basis onto their TIPPS account. Pop-up windows will inform the participants when an update is needed. In clinical settings, leg length is usually assessed as the measure between the anterior superior iliac spine and the medial malleolus (supine position), and is referred to as the "direct" clinical method.[40] The measurements will be performed on both legs and the average value will be used for the normalisation of step length. Additionally, the distance between the greater trochanter and the ground will be measured (standing position) to assess leg stiffness.[41] Body composition will be evaluated by bioelectrical impedance analysis (Tanita SC-240 MA). The proportion of fat mass will be included in the analyses as a potential confounder for the association between body mass and injury risk.

Data on exposure

Data on running practice will be collected using the TIPPS system.[32, 42] Required information in the sport activity report includes the type of activity, context, duration, subjectively perceived intensity, distance, shoe pair used, running surface (hard or soft), and whether the participant had experienced any pain during the session forcing him/her to reduce practice volume or intensity, or to interrupt the practice. Session intensity is determined using the Borg's rating of perceived exertion scale, a subjective 10-point scale.[43]

Data on outcome

The primary outcome is first-time RRI. A consensus definition of RRI in recreational runners has been recently published.[44] The definition of RRI is a "running-related (training or competition) musculoskeletal pain in the lower limbs that causes a restriction on or stoppage of running (distance, speed, duration, or training) for at least 7 days or 3 consecutive scheduled training sessions, or that requires the runner to consult a physician or other health professional."

In previous studies, an RRI was defined as "any physical pain located at the lower limbs or lower back region, sustained during or as a result of running practice and impeding planned running activity for at least 1 day" (time-loss definition).[15, 32, 36, 37, 42] All painful episodes reported by the participants during the follow-up will be assessed by a member of the research team according to each of the two definitions presented above. The consensus definition will be considered as the reference, while a sensitivity analysis will reveal if the results would be impacted when using the former definition of RRI.

Similarly to uploading a training session or competition, the TIPPS provides a complete yet easy to fill in questionnaire when reporting an injury. Information regarding the following is required: injury date, context, sports discipline, injury mechanism (acute or progressive), anatomical location, type of injury, description (free text field) and estimated return date. RRIs will be classified according to the Orchard Sports Injury Classification System version 10 (OSICS-10).[45] Injury severity will be measured in days of modified or interrupted training.

Follow-up

Given that the participants are required to practice running at least once a week, individual e-mail reminders will be sent to the participants who do not provide the system with any data for the preceding week. Personal phone calls will be made if the participants do not react to the e-mail reminders and if the reported information in either the training log or on the injury form is found to be inconsistent.

Participants reporting any injury will be systematically contacted by one of the investigators to verify completeness and coherence of the reported data, and to check if the episode qualifies as an RRI (as defined above). Participants who do not complete their entire running calendar with weekly information will be contacted by one of the investigators to ensure that a RRI is not the reason for non-compliance or dropping out. The intervention period will last six months, allowing enough time for the participants to cover a large distance with the study shoes.

Sample size

A sample size calculation for Cox regression was used to determine the number of participants needed for the primary hypothesis of the study. With an alpha of 0.05 and a power of 80%, an average injury rate of 30%,[15, 36, 37] an expected hazard rate ratio (HR)=1.50 between groups, 50% of participants randomised to each shoe group and an expected drop-out rate of 20%, the total number of participants required is 802.

Statistical analysis

Descriptive data for the personal, anthropometric, biomechanical and training-related characteristics will be presented as count and percentage for dichotomous variables, and as mean and standard deviation, or as median and range, respectively, for normally and non-normally distributed continuous variables. Average sport-related characteristics will be computed for each participant over their specific period of observation. Shock absorption properties (stiffness, N/mm) of the two types of shoes will be compared using a Student's t test.

Cox proportional hazards regressions will be used to compute the hazard rates in the exposure groups, using first-time injury as the primary outcome. Date of inclusion (baseline evaluation date) and date of injury or of censoring will be basic data used to calculate the time at risk, which is expressed in hours spent running and defined as the time-scale.[35] A participant will be right-censored if injury unrelated to running or severe disease caused a modification of the running plan, or at the end of follow-up. Reasons for right-censoring will be reported. The assumption of proportional hazards will be evaluated by log-minus-log plots.

Unadjusted Cox regressions will be performed to present the crude estimates of HRs for shoe model, body mass and other potential risk factors such as running biomechanics variables (see table 1) and training-related characteristics. Body mass is an exposure that can change over time (time-dependent covariate). This means that each participant could move between exposure states continuously (every month in our study). A delayed entry will be used in the unadjusted Cox regression model for body mass.[46]

Subsequently, the variables with a P value <0.200 will be included in the adjusted Cox regression analysis to determine whether shoe cushioning and/or body mass are associated with injury risk, controlling for potential confounders. The recommendation for using at least 10 injuries per predictor variable included in the Cox regression analysis will be strictly followed.[47]

Finally, to investigate if the effect of shoe cushioning on RRI risk is modified by body mass, a stratified analysis will be performed using the median value of body mass as cut-off. HRs and their 95% confidence intervals (CI) will be determined within each stratum.[48] All analyses will be performed using STATA/SE version 14.

DISCUSSION

It is common belief that shoe cushioning technology protects the runner against harmful consequences of repetitive high-load impacts. Therefore, heavier runners are generally advised to use footwear with adapted shock absorption properties. Surprisingly, few studies have investigated the impact of shoe cushioning on injury risk.[32, 33] These studies did not provide any evidence on the beneficial effect of increased shock absorption properties. However, none of them included anthropometric measures in their analyses. Also, one study compared different types of insoles added in the shoes,[33] while the other compared two versions of a standard running shoe with a limited difference in midsole hardness (~15%).[32] Other study limitations such as the sample size (n<250)[32] or the study population (Royal Air Force recruits)[33] suggest that these results should be interpreted with caution. The evidence on the association between running shoe cushioning and RRI is still poor and inconclusive. One of the main reasons is the practical constraint of investigations trying to combine biomechanical analyses with a long-term prospective follow-up in a large number of runners.[11] This study is the first randomised controlled trial investigating the influence of shoe cushioning on RRI risk including an evaluation of running technique in all participants. The results will provide information on the real benefits provided by additional cushioning, as well as on the mechanisms that might explain any potential preventive effect.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the Declaration of Helsinki and the Medical Research Involving Human Subjects Act. Also, the study protocol (Ref: 201701/02 v1.1) was approved by the National Ethics Committee for Research (www.cner.lu). Written informed consent will be obtained from all participants (Supplementary file 4). All collected data will be stored electronically using a coding system. This will ensure that the data is used in the strictest confidence and will not reveal the identity of the participants. Collected raw data will not be passed on to unauthorised third parties. Results presented or published in articles and reports will be depicted in general terms, to maintain participant anonymity. Electronic data will be stored on a secure server in data files only accessible to the project leader and co-investigators of the project. A notification of this study was sent to the National Data Protection Agency (CNPD). Study results will be submitted for publication in peer-reviewed journals and for presentation at international conferences. Furthermore, we aim to disseminate our results through popular specialised magazines and websites.

Contributors - LM, ND, AU and DT contributed to the study conception and study design. LM is the main investigator, wrote the article with input from other investigators, and will be responsible for the acquisition and analysis of the data. ND will be responsible for the shoe design, production and testing. LM and DT will be responsible for data interpretation and manuscript drafting. ND, AU and DT commented on the various versions of the study protocol. All authors approved the final manuscript.

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Competing interests – A research partnership agreement was signed between Decathlon and the Luxembourg Institute of Health (LIH). ND is employed at Decathlon SA. Decathlon will not be involved in the collection, management, analysis and interpretation of data. LM, DT and AU may not gain or lose financially from the results of the study in any way.

Ethics approval - All procedures were approved by the National Ethics Committee for Research (Ref: 201701/02 v1.1).

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486 **FIGURE LEGEND**

488 Figure 1: Trial design.

490 **SUPPLEMENTARY FILES**

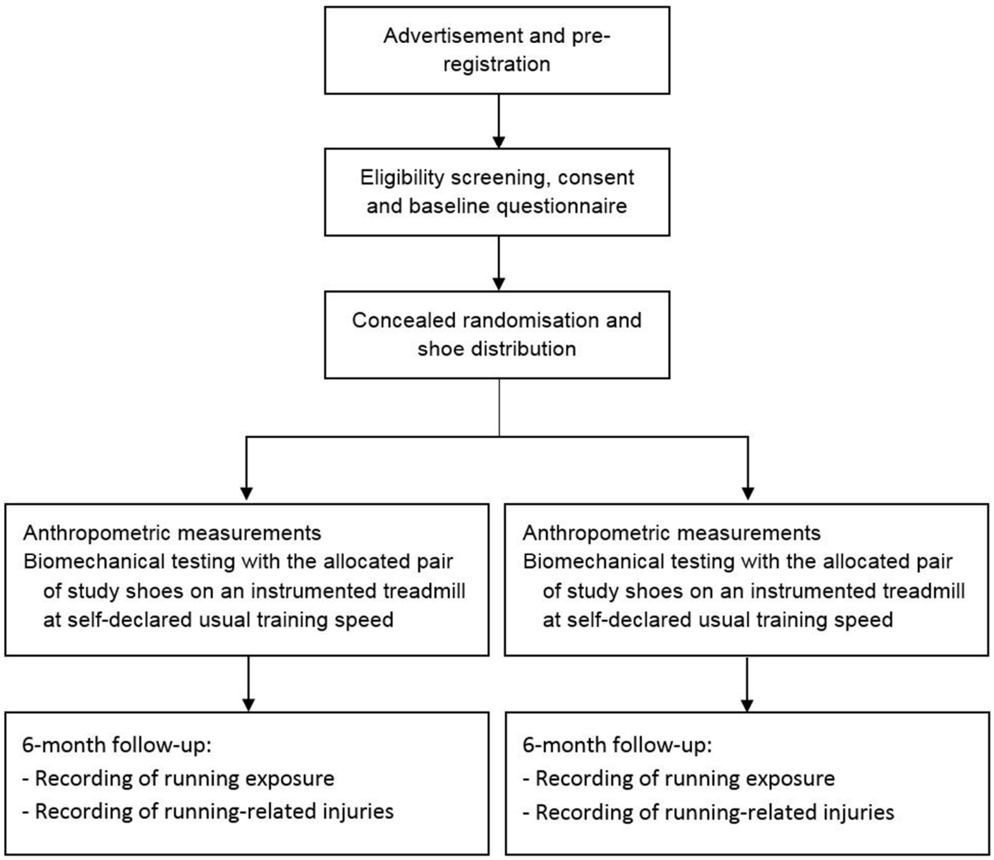
492 Supplementary file 1: SPIRIT Checklist

494 Supplementary file 1: Study schedule

496 Supplementary file 3: Risk of sport participation form

498 Supplementary file 4: Informed consent

Figure 1: Trial Design



Trial design

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Pages 2 & 7: clinicaltrials.gov (NCT03115437)
	2b	All items from the World Health Organization Trial Registration Data Set	/
Protocol version	3	Date and version identifier	Page 7
Funding	4	Sources and types of financial, material, and other support	Page 15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 15
	5b	Name and contact information for the trial sponsor	Page 1 & 15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 15

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n.a.
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Pages 4 and 5
	6b	Explanation for choice of comparators	Pages 5 and 4
Objectives	7	Specific objectives or hypotheses	Page 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 7 and 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 11-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 11-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n.a.

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 9 and 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 and Suppl. file 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 8
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Pages 9 to 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 11
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pages 12 and 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Pages 12 and 13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Pages 12 and 13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	/
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	/
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	/
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Pages 14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	/
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 14
	31b	Authorship eligibility guidelines and any intended use of professional writers	/
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 4

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

Supplementary file 2: Schedule of enrolment, interventions, and assessments for the study

	STUDY PERIOD							
	Enrolment	**Allocation**	**Post-allocation: For every sport activity**					**Close-out**
TIMEPOINT	***-t₁***	**0**	t_1	t_2	t_3	t_4	***etc.***	***6 Months***
ENROLMENT								
Eligibility screen	X							
Informed consent	X							
Baseline Questionnaire	X	X						
Allocation		X						
Shoe distribution		X						
Running analysis		X						
INTERVENTIONS								
[Intervention A]								
[Intervention B]								
ASSESSMENTS								
Running experience	X	X						
Running regularity	X	X						
Typical running frequency	X	X						
Typical running distance	X	X						
Training running speed	X	X						
Type of running	X	X						
Competition participation	X	X						
Last event distance	X	X						
Favourite running distance	X	X						
Best time on 5 km / 10km	X	X						
Previous injury	X	X						

Height	X	X						
Body mass	X	X						
Leg length	X	X						
% fat tissue	X	X						
Step frequency	X	X						
Contact time	X	X						
Flight time	X	X						
Duty factor	X	X						
Step length	X	X						
Vertical Impact Peak Force	X	X						
Peak Vertical Force	X	X						
Vertical Instantaneous Loading Rate	X	X						
Vertical Average Loading Rate	X	X						
Peak Power	X	X						
Time to Peak Force	X	X						
Leg stiffness	X	X						
Vertical stiffness	X	X						
Sports discipline			X	X	X	X	etc.	
Duration			X	X	X	X	etc.	
Distance (if applicable)			X	X	X	X	etc.	
Perceived Exertion			X	X	X	X	etc.	
Shoe used (if running)			X	X	X	X	etc.	
Surface (if running)			X	X	X	X	etc.	
Pain*			X	X	X	X	etc.	
Injury**			X	X	X	X	etc.	

*The pain did not stop the participant from continuing normal training
**The participants had to adapt or interrupt their training accordingly

Supplementary file 4 : Questionnaire on risk of sport participation

1. Past medical history, have you had:
    1.1 Severe cardiac arrythmia?
    1.2 Myocardial infarction?
    1.3 Heart surgery?
    1.4 Intracardiac catheter?
    1.5 Coronary angioplasty (dilatation by balloon, stenting)?
    1.6 Pacemaker or heart defibrillator?
    1.7 Cardiac insufficiency?
    1.8 Heart transplantation?
    1.9 Congenital heart defect?
2. Past and present complaints
    2.1 Chest pain / discomfort during physical exertion?
    2.2 Dyspnea (uncommon breathlessness)?
    2.3 Dizziness/unconsciousness?
    2.4 Palpitations, tachycardia, pulse irregularities?
    2.5 Intake of any cardiac drugs?
3. Other disorders
    3.1 Muscular or articular complaints?
    3.2 Other drugs?
    3.3 Insecurity during physical exertion?
    3.4 For females: Pregnancy?
4. Cardiovascular risk factors
    4.1 Are you male over 45 years?
    4.2 Are you female over 55 years or you hava had a hysterectomy or you are menopausal?
    4.3 Smoker (active / in the past 10 years)?
    4.4 Your blood pressure is over 140/90 mmHg or you take antihypertensive drugs?
    4.5 Your cholesterol level is over 240 mg/dl?
    4.6 Myocardial infarction, stroke, marfan disease or sudden cardiac death in the family ? (Father resp. brother before age of 55 years/ Mother resp. sister before 65 years)?
    4.7 You are diabetic or you take antidiabetic drugs?
    4.8 Sports activity less than 90 min/week?
    4.9 You have a Body Mass Index (BMI) over 30 ?

Free Informed Consent

Title:
Institution:
Project manager:
Research assistant:
Head of unit:

1. I declare to have read the above-described information and accept to voluntarily participate in the study “Effects of bodyweight and shoe cushioning on injury risk and running biomechanics: A randomised control trial” conducted by the SMRL.
2. I accept that my data shall be used and communicated to the commercial partner for strictly scientific purposes once it has been pseudonymised (coded).
3. I received a copy of the present signed informed consent document, as well as the general information intended for athlete participants. I received a clear description of the purpose and the nature of the study and I am aware of what is expected of me as a participant in this study. I have had enough time and the opportunity to ask questions about the study; all my questions have been met with a satisfactory answer.
4. I am free to retire from the study at any time without justification. By doing so I will not suffer any material or moral damage.
5. I agree that the results of this study can be subject to public talks or scientific publication.
6. I voluntarily consent to participate in this study and I fully understand what kind of data will be gathered during the study.
7. I preserve/abide the rights of access, deletion or modification of my personal data. Any personal information will be kept confidential and protected in agreement with the modified personal data protection act of Augept 2nd 2002. I can exercise that right via the project manager.

The responding signatory freely consents to participate in the above mentioned study

Name and First Name of the respondent: ....

Signature of the respondent: ……………………………………………………………………………

Name and signature of the project manager: …………………………………………………………..

Place and date: ………………………...

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Shoe cushioning, body mass and running biomechanics as risk factors for running injury: a study protocol for a randomised controlled trial

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TITLE PAGE

Title:

Shoe cushioning, body mass and running biomechanics as risk factors for running injury: a study protocol for a randomised controlled trial

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ABSTRACT

Introduction: Repetitive loading of the musculoskeletal system is suggested to be involved in the underlying mechanism of the majority of running-related injuries (RRI). Accordingly, heavier runners are assumed to be at a higher risk of RRI. The cushioning system of modern running shoes is expected to protect runners again high impact forces, and therefore, RRI. However, the role of shoe cushioning in injury prevention remains unclear. The main aim of this study is to investigate the influence of shoe cushioning and body mass on RRI risk, while exploring simultaneously the association between running technique and RRI risk.

Methods and analysis: This double-blinded randomised controlled trial will involve about 800 healthy leisure-time runners. They will randomly receive one of two running shoe models that will differ in their cushioning properties (i.e. stiffness) by ~35%. The participants will perform a running test on an instrumented treadmill at their preferred running speed at baseline. They will then be followed-up prospectively over a 6-month period, during which they will self-report all their sports activities as well as any injury in an internet-based database TIPPS (Training and Injury Prevention Platform for Sports). Cox regression analyses will be used to compare injury risk between the study groups and to investigate the association between training, biomechanical and anatomical risk factors, and injury risk.

Ethics and dissemination: The study was approved by the National Ethics Committee for Research (Ref: 201701/02 v1.1). Outcomes will be disseminated through publications in peer-reviewed journals, presentations at international conferences, as well as articles in popular magazines and on specialised websites.

Trial registration number: NCT03115437

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Double-blinded randomised controlled trial (assessor and participant blinding) and intention-to-treat analysis.
- This study compares 2 shoe versions with widely differing cushioning properties while remaining within the cushioning range of models available on the market.
- A biomechanical analysis will be performed for each participant prior to the 6-month follow-up, which allows to investigate the association between running biomechanics and injury risk in a large cohort of runners.
- The running test will be carried out on a treadmill using a standardised protocol, which might not be reflective of the participants' habitual training conditions.

INTRODUCTION

Running is an increasingly popular form of physical activity. From a public health perspective, the promotion of leisure-time running might be a powerful strategy to combat the pandemic of physical inactivity worldwide,[1] and its consequence on non-communicable diseases.[2] Although regular running activity has a massive beneficial impact on health,[3] it also generates a relatively high number of injuries, especially at the lower limb.[4] The risk of sustaining a running-related injury (RRI) cancels out part of the benefits of running practice, since the long term consequences of injury might include, among others, increased risk of osteoarthritis,[5] a reduction of physical activity,[6] as well as an increase in health care costs.[7, 8] RRI incidence has remained high during the last 40 years, with an overall incidence rate ranging between 18.2% and 92.4%.[9] The role of footwear on RRI risk has been strongly emphasized ever since jogging became popular in the 1970s, but there is currently no evidence that developments in running shoe technology and new concepts regularly emerging on the market have helped to tackle the RRI burden.[10-12]

Most RRI are overuse injuries, as they develop progressively over the kilometres run. The aetiology of these injuries is multifactorial,[13] which implies that to understand the mechanisms leading to injury, a holistic approach is warranted, including the study of a large set of potential risk factors. These factors could be classified as being related to training characteristics, running mechanics and anatomy of the runners. Some authors suggested that anatomical and biomechanical factors influence the tolerance to physical strain and thus the relationship between training load and injury occurrence.[14, 15]

Biological tissues such as bones, muscles and tendons can endure a certain amount of stress, provided that the product of stress level (e.g. intensity, external load) and the number of repetitions within a certain time period (e.g. strides, training sessions) remains below a threshold that is specific to each structure.[14] In running, the ground reaction force is the main external stress that acts on the body. Vertical ground reaction force (VGRF) is a biomechanical factor that has been extensively studied in

running.[16, 17] A recent meta-analysis found that the loading rate of the vertical ground reaction force was higher in patients with a history of stress fracture.[16] High impact-related variables were shown to increase the risk of bony and soft tissue injuries.[17] Moreover, running retraining interventions have proven their efficiency in modifying some VGRF parameters and decreasing pain, which suggest that running retraining represents an interesting paradigm to treat RRI.[18-20] Other biomechanical factors such as step length,[21] step frequency [22] or leg stiffness [23] have previously been suggested as potential biomechanical risk factors for RRI, yet no causal relationship has been established.

Since running biomechanics are associated with injury risk, any effect of shoe features on the running pattern and VGRF parameters deserve attention. Given that repetitive loading of the musculoskeletal system is an injury risk factor, cushioning has been one of the most extensively investigated shoe features. The shock absorption properties of footwear mainly result from the materials used in the sole (i.e. their type, density, structure and combination), as well as from the geometry of the shoe (i.e. the midsole thickness and the design of inserts). One of the most popular approaches has been to change the hardness of the shoe midsole.[24-26] Overall, the studies investigating the effect of shoe cushioning on VGRF did not provide consistent results. In theory, peak impact forces should be reduced by softer or more compliant shoes,[27] which was indeed confirmed in some in vivo studies.[28, 29] Conversely, some investigations did not find any effect of cushioning,[30] or reported increased peak impact forces in softer shoes.[24, 31] Recently, a large cross sectional study revealed that softer midsole hardness was associated with higher vertical force impact peak.[24] Unfortunately, very few studies have investigated the association between shoe cushioning and injury risk.[32, 33] In a previous randomised controlled trial, midsole hardness was not associated with RRI risk. However, the difference in shoe stiffness between the shoe conditions was limited (15%).[32] Therefore, the role of shoe cushioning systems in RRI prevention remains unclear.

Body mass index (BMI) has been associated with injury risk in novice,[34, 35] as well as in recreational runners,[32] though other results suggest a protective effect of BMI.[9] It is common belief that individuals with higher BMI have a higher injury risk, because of the increased physical stress that results from extra body weight. Surprisingly, body mass as such has hardly ever been considered as a potential risk factor for running injury.[9]

Surprisingly, the literature on the association between single shoe features and RRI risk is still poor.[11, 36, 37] Until now, no relationship has been found between the cushioning properties of modern running shoes and RRI risk,[32] but body mass should be taken into account here. Therefore, the main purpose of this study is to investigate the association between shoe cushioning and body mass on the one hand, and RRI risk on the other hand in recreational runners. The secondary aims are to identify which of the running technique-related characteristics (timing variables and VGRF parameters) are associated with injury risk, as well as with the cushioning properties of the shoes. Shoe cushioning will be characterised by the stiffness at the heel (N/mm) and quantified by standardised impact test.[38] The following hypotheses (H) will be tested:

H1. Running shoes with greater stiffness are associated with a higher injury risk in leisure-time runners.

H2. High body mass is associated with a higher injury risk in leisure-time runners.

H3. Runners with a high body mass experience a lower injury risk in shoes with greater stiffness.

H4. A higher step length, a lower step frequency, and higher vertical loading rate are associated with a higher injury risk.

H5. Running shoes with greater stiffness will be associated with higher vertical loading rate and a shorter contact time.

H6. High body mass will be associated with higher vertical loading rate, increased contact time, increased duty factor, and decreased step frequency.

Furthermore, exploratory risk factor analyses will be performed on the biomechanical variables obtained from the running analysis, anthropometric measurements, running experience, and habitual running speed. The focus of the analyses is the effect modification of body mass and other above mentioned risk factors on the association between shoe cushioning and injury risk.

METHODS AND ANALYSIS

Trial design

The design of this study is a randomised controlled trial with a 6-month follow-up and a biomechanical analysis of running pattern at baseline. The study is based on the comparison between 2 running shoe prototypes, which only differ with respect to the cushioning (i.e. stiffness). The cushioning properties of both shoe versions are within the range of those from available models on the market. Running footwear is provided by a renowned sport equipment manufacturer. The main outcome is RRI (cf. definition below). The participants as well as the assessors are blinded to group allocation. The design of the trial is illustrated in Figure 1. The protocol conforms to the Recommendations for Interventional Trials (SPIRIT) and has been registered on https://clinicaltrials.gov/ (NCT03115437, 11/04/2017).

Insert Figure 1 about here

Study population

The target population is leisure-time runners, regardless of running experience, fitness level, or body mass. Participants will be recruited through advertisements in local newspapers, social media, running magazines and press releases within the country during the months of September 2017 to January 2018. Healthy volunteers will be considered eligible if they are aged between 18 and 65 years and capable of performing 15 minutes of consecutive running. Volunteers will be excluded in case of any contraindication to perform running activity, prior (<12 months) surgery or major trauma to the lower limbs or lower back region, any running impeding injury over the previous month, or use of orthopaedic insoles for running activities. Additionally, the participants will have to agree on the following requirements: 1) to practice running at least once a week, 2) to use the provided study shoes for all their running sessions, and 3) to report, at least once per week, all sports activities, as well as any injury or pain experienced during the follow-up period on an internet-based database called TIPPS (Training and Injury Prevention Platform for Sports, www.tipps.lu). Volunteers first have to create a personal account on TIPPS, pre-register to the study via their personal account, and answer an online inclusion/exclusion questionnaire as well as a baseline questionnaire. Answers to both questionnaires will be assessed by the investigators during the initial visit.

Randomisation

Participants must understand and agree on the randomized design of the study. Those who meet the eligibility criteria and sign the informed consent form will be randomly allocated to one of the two study arms. They will be stratified according to their sex, which is known to influence body mass as well as many other anthropometric characteristics. Therefore, two pre-established randomisation lists (block size = 40) will be prepared by a statistician not involved in any other part of the study before the beginning of the recruitment. To ensure allocation concealment, the study groups and shoes will be coded and the randomisation lists will be uploaded in the TIPPS system by an IT specialist who will not be involved in any other part of the study. Then, the TIPPS system will provide the investigator in charge of the recruitment with a study group number for each participant, according to the randomisation lists. The investigator will upload the shoe number according to shoe size chosen and study arm so that a cross validation will be performed by the electronic system. The investigators in charge of the recruitment, the follow-up and data quality check, as well as the participants, will be blinded regarding the shoe version distributed. The shoe code will be broken after completion of data analysis.

Intervention

The study shoes are prototypes and will be anonymized for the purpose of this trial. The sole of the shoes will be customized so that the two running shoe prototypes will be exactly the same (same midsole, same outsole, same upper), except for their cushioning properties which will differ by about

35%, while remaining within the range of the models available on the market (stiffness: ~53-97 N/mm). The differences in cushioning properties between shoe versions will be created by modifying the midsole material, i.e. chemistry, density, and therefore the hardness of the Ethylene Vinyl Acetate (EVA) foam. In order to provide accurate data on the technical specifications (i.e. shoe stiffness) of each prototype, a set of 40 shoes (10 pairs per condition) will be tested for stiffness properties by the manufacturer according to a standardized protocol (Impact test: ASTM1614, Procedure A).[38]

Data collection

Baseline questionnaire

During the online registration process, the participants have to fill in a baseline questionnaire to report information regarding running experience, training habits, recent running competitions performed and injury history. A standardised questionnaire concerning the risk of sports participation must also be completed by the volunteers (Supplementary file 1). Every participant responding positively to any of the symptom-based questions or presenting more than one cardiovascular risk factor will be invited for a clearance check by a sports medical doctor prior to the test.

Biomechanical testing

The biomechanical running analysis will be performed on an instrumented treadmill (M-Gait, Motekforce Link Amsterdam, The Netherlands) in the randomly allocated study shoes. The test (10 minutes) consists of a 5-minute warm-up followed by a 5-minute run at the self-declared preferred (habitual) running speed. Two records of 45 seconds will be obtained at a sampling rate of 1 kHz over the last 2 minutes of the test. No data will be recorded during the first 8 minutes, which was shown to be enough time to provoke short-term adaptations of running style with respect to the shoe type.[25, 39] The main biomechanical variables of interest are presented in table 1.

Table 1: Biomechanical variables of interest.

Variable	Abbreviation	Unit	Normalization

Step frequency	SF	[Steps.min^{-1}]	/
Contact time	CT	[ms]	/
Flight time	FT	[ms]	/
Duty factor	DF	[%]	/
Step length	SL	[m]	[%LL]
Vertical Impact Peak Force	VIPF	[N]	[N.kg^{-1}]
Peak Vertical Force	PVF	[N]	[N.kg^{-1}]
Vertical Instantaneous Loading Rate	VILR	[N.s^{-1}]	[N.kg^{-1}.s^{-1}]
Vertical Average Loading Rate	VALR	[N.s^{-1}]	[N.kg^{-1}.s^{-1}]
Peak Power	PP	[W]	[W.kg^{-1}]
Time to Peak Force	TPF	[ms]	/
Leg stiffness	Kleg	(kN/m)	/
Vertical stiffness	Kvert	(kN/m)	/

N: Newton, min: minute, ms: millisecond, m: meter, LL: leg length, kg: kilogram, W: Watt.

Anthropometric measures

Body mass and height of each participant will be measured barefoot and in running clothes before the treadmill running test. Also, the participants will have to report their body mass on a monthly basis onto their TIPPS account. Pop-up windows will inform the participants when an update is needed. In clinical settings, leg length is usually assessed as the measure between the anterior superior iliac spine and the medial malleolus (supine position), and is referred to as the "direct" clinical method.[40] The measurements will be performed on both legs and the average value will be used for the normalisation of step length. Additionally, the distance between the greater trochanter and the ground will be measured (standing position) to assess leg stiffness.[41] Body composition will be evaluated by bioelectrical impedance analysis (Tanita SC-240 MA). The proportion of fat mass will be included in the analyses as a potential confounder for the association between body mass and injury risk.

Data on exposure

Data on running practice will be collected using the TIPPS system.[32, 42] Required information in the sport activity report includes the type of activity, context, duration, subjectively perceived intensity, distance, shoe pair used, running surface (hard or soft), and whether the participant had experienced any pain during the session forcing him/her to reduce practice volume or intensity, or to interrupt the practice. Session intensity is determined using the Borg's rating of perceived exertion scale, a subjective 10-point scale.[43]

Data on outcome

The primary outcome is the first RRI occurring during the follow-up. A consensus definition of RRI in recreational runners has been recently published.[44] The definition of RRI is a "running-related (training or competition) musculoskeletal pain in the lower limbs that causes a restriction on or stoppage of running (distance, speed, duration, or training) for at least 7 days or 3 consecutive scheduled training sessions, or that requires the runner to consult a physician or other health professional."

In previous studies, an RRI was defined as "any physical pain located at the lower limbs or lower back region, sustained during or as a result of running practice and impeding planned running activity for at least 1 day" (time-loss definition).[15, 32, 36, 37, 42] All painful episodes reported by the participants during the follow-up will be assessed by a member of the research team according to each of the two definitions presented above. The consensus definition will be considered as the reference, while a sensitivity analysis will reveal if the results would be impacted when using the former definition of RRI.

Similarly to uploading a training session or competition, the TIPPS provides a complete yet easy to fill in questionnaire when reporting an injury. Information regarding the following is required: injury date, context, sports discipline, injury mechanism (acute or progressive), anatomical location, type of injury, description (free text field) and estimated return date. RRIs will be classified according to the

Orchard Sports Injury Classification System version 10 (OSICS-10).[45] Injury severity will be measured in days of modified or interrupted training.

Follow-up

Given that the participants are required to practice running at least once a week, individual e-mail reminders will be sent to the participants who do not provide the system with any data for the preceding week. Personal phone calls will be made if the participants do not react to the e-mail reminders and if the reported information in either the training log or on the injury form is found to be inconsistent.

Participants reporting any injury will be systematically contacted by one of the investigators to verify completeness and coherence of the reported data, and to check if the episode qualifies as an RRI (as defined above). Participants who do not complete their entire running calendar with weekly information will be contacted by one of the investigators to ensure that a RRI is not the reason for non-compliance or dropping out. The intervention period will last six months, allowing enough time for the participants to cover a large distance with the study shoes.

Sample size

A sample size calculation for Cox regression was used to determine the number of participants needed for the primary hypothesis of the study. With an alpha of 0.05 and a power of 80%, an average injury rate of 30%,[15, 36, 37] an expected hazard rate ratio (HR)=1.50 between groups, 50% of participants randomised to each shoe group and an expected drop-out rate of 20%, the total number of participants required is 802.

Statistical analysis

Descriptive data for the personal, anthropometric, biomechanical and training-related characteristics will be presented as count and percentage for dichotomous variables, and as mean and standard deviation, or as median and range, respectively, for normally and non-normally distributed continuous variables. Average sport-related characteristics will be computed for each participant over their specific period of observation. Shock absorption properties (stiffness, N/mm) of the two types of shoes will be compared using a Student's t test.

Cox proportional hazards regressions will be used to compute the hazard rates in the exposure groups, using first-time injury as the primary outcome. Date of inclusion (baseline evaluation date) and date of injury or of censoring will be basic data used to calculate the time at risk, which is expressed in hours spent running and defined as the time-scale.[35] A participant will be right-censored if injury unrelated to running or severe disease caused a modification of the running plan, or at the end of follow-up. Reasons for right-censoring will be reported. The assumption of proportional hazards will be evaluated by log-minus-log plots.

Unadjusted Cox regressions will be performed to present the crude estimates of HRs for shoe model, body mass and other potential risk factors such as running biomechanics variables (see table 1) and training-related characteristics. Body mass is an exposure that can change over time (time-dependent covariate). This means that each participant could move between exposure states continuously (every month in our study). A delayed entry will be used in the unadjusted Cox regression model for body mass.[46]

Subsequently, the variables with a P value <0.200 will be included in the adjusted Cox regression analysis to determine whether shoe cushioning and/or body mass are associated with injury risk, controlling for potential confounders. The recommendation for using at least 10 injuries per predictor variable included in the Cox regression analysis will be strictly followed.[47]

Finally, to investigate if the effect of shoe cushioning on RRI risk is modified by body mass, a stratified analysis will be performed using the median value of body mass as cut-off. HRs and their 95% confidence intervals (CI) will be determined within each stratum.[48] All analyses will be performed using STATA/SE version 14.

DISCUSSION

It is common belief that shoe cushioning technology protects the runner against harmful consequences of repetitive high-load impacts. Therefore, heavier runners are generally advised to use footwear with adapted shock absorption properties. Surprisingly, few studies have investigated the impact of shoe cushioning on injury risk.[32, 33] These studies did not provide any evidence on the beneficial effect of increased shock absorption properties. However, none of them included anthropometric measures in their analyses. Also, one study compared different types of insoles added in the shoes,[33] while the other compared two versions of a standard running shoe with a limited difference in midsole hardness (~15%).[32] Other study limitations such as the sample size (n<250)[32] or the study population (Royal Air Force recruits)[33] suggest that these results should be interpreted with caution. The evidence on the association between running shoe cushioning and RRI is still poor and inconclusive. One of the main reasons is the practical constraint of investigations trying to combine biomechanical analyses with a long-term prospective follow-up in a large number of runners.[11] This study is the first randomised controlled trial investigating the influence of shoe cushioning on RRI risk including an evaluation of running technique in all participants. The results will provide information on the real benefits provided by additional cushioning, as well as on the mechanisms that might explain any potential preventive effect.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the Declaration of Helsinki and the Medical Research Involving Human Subjects Act. Also, the study protocol (Ref: 201701/02 v1.1) was approved by the National Ethics Committee for Research (www.cner.lu). Written informed consent will be obtained from all participants (Supplementary file 2). All collected data will be stored electronically using a coding system. This will ensure that the data is used in the strictest confidence and will not reveal the identity of the participants. Collected raw data will not be passed on to unauthorised third parties. Results presented or published in articles and reports will be depicted in general terms, to maintain participant anonymity. Electronic data will be stored on a secure server in data files only accessible to the project leader and co-investigators of the project. A notification of this study was sent to the National Data Protection Agency (CNPD). Study results will be submitted for publication in peer-reviewed journals and for presentation at international conferences. Furthermore, we aim to disseminate our results through popular specialised magazines and websites.

Contributors - LM, ND, AU and DT contributed to the study conception and study design. LM is the main investigator, wrote the article with input from other investigators, and will be responsible for the acquisition and analysis of the data. ND will be responsible for the shoe design, production and testing. LM and DT will be responsible for data interpretation and manuscript drafting. ND, AU and DT commented on the various versions of the study protocol. All authors approved the final manuscript.

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Competing interests – A research partnership agreement was signed between Decathlon and the Luxembourg Institute of Health (LIH). ND is employed at Decathlon SA. Decathlon will not be involved in the collection, management, analysis and interpretation of data. LM, DT and AU may not gain or lose financially from the results of the study in any way.

Ethics approval - All procedures were approved by the National Ethics Committee for Research (Ref: 201701/02 v1.1).

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487 **FIGURE LEGEND**

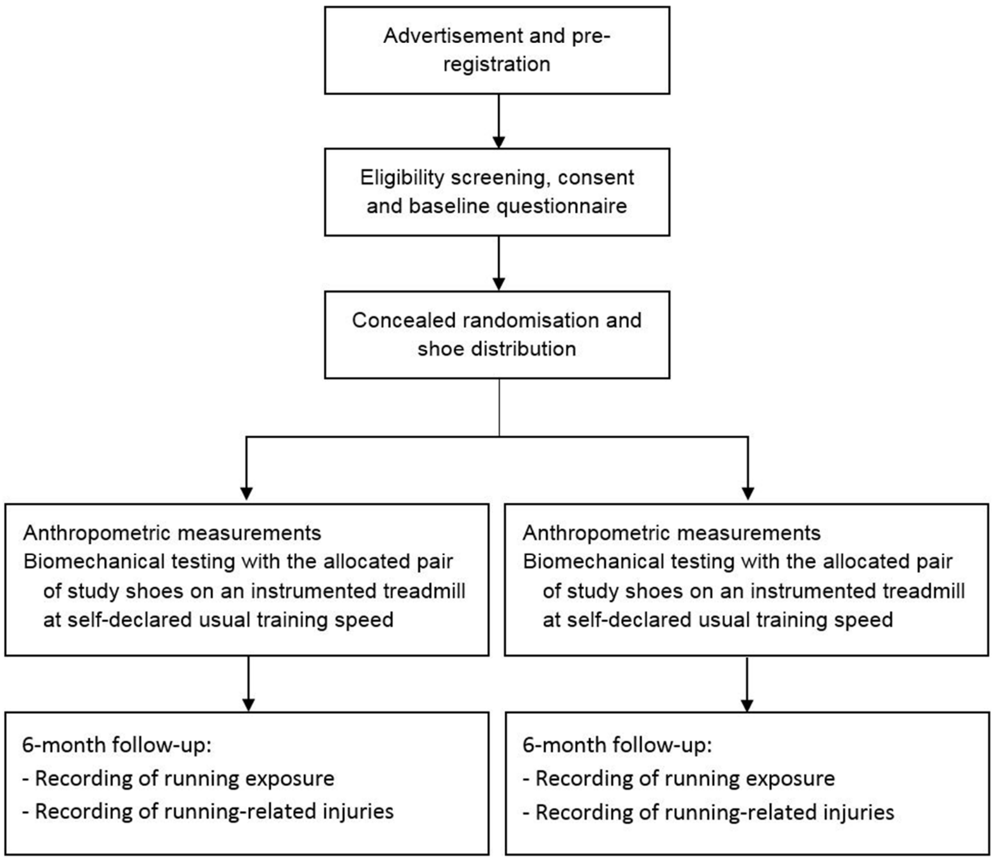
Figure 1: Trial design.

SUPPLEMENTARY FILES

Supplementary file 1: Risk of sport participation form

Supplementary file 2: Informed consent

Figure 1: Trial Design



Trial design

Supplementary file 4 : Questionnaire on risk of sport participation

1. Past medical history, have you had:
   - 1.1 Severe cardiac arrythmia?
   - 1.2 Myocardial infarction?
   - 1.3 Heart surgery?
   - 1.4 Intracardiac catheter?
   - 1.5 Coronary angioplasty (dilatation by balloon, stenting)?
   - 1.6 Pacemaker or heart defibrillator?
   - 1.7 Cardiac insufficiency?
   - 1.8 Heart transplantation?
   - 1.9 Congenital heart defect?
2. Past and present complaints
   - 2.1 Chest pain / discomfort during physical exertion?
   - 2.2 Dyspnea (uncommon breathlessness)?
   - 2.3 Dizziness/unconsciousness?
   - 2.4 Palpitations, tachycardia, pulse irregularities?
   - 2.5 Intake of any cardiac drugs?
3. Other disorders
   - 3.1 Muscular or articular complaints?
   - 3.2 Other drugs?
   - 3.3 Insecurity during physical exertion?
   - 3.4 For females: Pregnancy?
4. Cardiovascular risk factors
   - 4.1 Are you male over 45 years?
   - 4.2 Are you female over 55 years or you hava had a hysterectomy or you are menopausal?
   - 4.3 Smoker (active / in the past 10 years)?
   - 4.4 Your blood pressure is over 140/90 mmHg or you take antihypertensive drugs?
   - 4.5 Your cholesterol level is over 240 mg/dl?
   - 4.6 Myocardial infarction, stroke, marfan disease or sudden cardiac death in the family ? (Father resp. brother before age of 55 years/ Mother resp. sister before 65 years)?
   - 4.7 You are diabetic or you take antidiabetic drugs?
   - 4.8 Sports activity less than 90 min/week?
   - 4.9 You have a Body Mass Index (BMI) over 30 ?

Free Informed Consent

Title:
Institution:
Project manager:
Research assistant:
Head of unit:

1. I declare to have read the above-described information and accept to voluntarily participate in the study "Effects of bodyweight and shoe cushioning on injury risk and running biomechanics: A randomised control trial" conducted by the SMRL.
2. I accept that my data shall be used and communicated to the commercial partner for strictly scientific purposes once it has been pseudonymised (coded).
3. I received a copy of the present signed informed consent document, as well as the general information intended for athlete participants. I received a clear description of the purpose and the nature of the study and I am aware of what is expected of me as a participant in this study. I have had enough time and the opportunity to ask questions about the study; all my questions have been met with a satisfactory answer.
4. I am free to retire from the study at any time without justification. By doing so I will not suffer any material or moral damage.
5. I agree that the results of this study can be subject to public talks or scientific publication.
6. I voluntarily consent to participate in this study and I fully understand what kind of data will be gathered during the study.
7. I preserve/abide the rights of access, deletion or modification of my personal data. Any personal information will be kept confidential and protected in agreement with the modified personal data protection act of August 2nd 2002. I can exercise that right via the project manager.

The responding signatory freely consents to participate in the above mentioned study

Name and First Name of the respondent: ....

Signature of the respondent: ……………………………………………………………………………

Name and signature of the project manager: ……………………………………………………….....

Place and date: ……………………………………………………………………………………………..